

Clinical Communications

Sensitization phenotypes in immediate reactions to piperacillin-tazobactam

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Clinical Implications

- Little is known about immediate hypersensitivity to piperacillin-tazobactam (PPZ-TZB). We describe 3 possible sensitization phenotypes in patients with immediate reactions to PPZ-TZB: (1) to the beta-lactam ring, (2) to the aminopenicillin side chain, and (3) selective to PPZ-TZB.

Piperacillin (PPZ) is an ureidopenicillin, with a broad spectrum of activity against Gram positive, Gram negative, and aerobic organisms, including *Pseudomonas aeruginosa*.¹ It is used in combination with tazobactam (TZB), a beta-lactamase inhibitor. The most commonly described adverse reactions are diarrhea, nausea, vomiting, and rashes. Type I hypersensitivity reactions have been described, including urticaria, angioedema, anaphylaxis, and bronchospasm.¹ There are very few reports of IgE-mediated reactions diagnosed by skin tests (STs), serum specific IgE, or drug provocation tests (DPTs),¹⁻³ and most are case reports. Consequently, the usefulness of diagnostic tests and patterns of cross-reactivity with other beta-lactam (BL) antibiotics are unknown. We aimed to perform a retrospective analysis evaluating all patients diagnosed with immediate reactions due to PPZ-TZB that were recorded in our database.

Patients were included if they had symptoms compatible with type I reactions of mast cell/basophil-mediated release after the administration of PPZ-TZB and a final diagnosis of hypersensitivity to PPZ-TZB. Anaphylactic reactions were diagnosed according to Sampson et al.⁴

STs were performed with reagents and drugs specified in Table I.⁵⁻⁷ Patients with negative STs with PPZ-TZB underwent DPTs⁸ up to a therapeutic dose. In patients with STs exclusively positive with PPZ-TZB, DPTs with other BLs were performed. Specific IgE to penicilloyl G and amoxicilloyl was performed following the manufacturer's instructions (ImmunoCAP system; ThermoFisher, Uppsala, Sweden). A value >0.35 kU/L was considered positive. DPT decisions were unaffected by specific IgE results.

The study was approved by the local Ethics Committee (Ref. 202002439).

Between 2009 and 2019, 11 patients (6 males, 54.5%) fulfilled the selection criteria. The mean age was 61 years (median, 65 years). Indications to be treated with PPZ-TZB were

diverticulitis, infectious colitis, Fournier gangrene, urinary sepsis, febrile neutropenia, pancreatitis, acute myeloblastic leukemia, respiratory infections, and other unspecified infectious diseases. No patient received PPZ-TZB for cystic fibrosis. Reactions were urticaria in 6 cases (54.5%) and anaphylaxis in 5 (45.5%) (Table II). In 5 of 11 patients, specific IgE determinations were checked. Three patients (27.3%) had positive specific IgE to penicilloyl G and/or amoxicilloyl. All of them had positive STs with BLs (Table II).

STs with PPZ-TZB were positive in 8 patients (72.7%): one positive prick test. Patient 1 had a systemic reaction when performing the intradermal reaction with benzylpenicilloyl-octa-L-lysine (BP-OL), so STs and DPTs with PPZ-TZB were not performed; this patient had positive specific IgE to both penicilloyl G and amoxicilloyl. Two patients (18.2%) were diagnosed by DPTs (both had acute urticaria; none required epinephrine).

STs with other BLs were performed on all patients except patient 1. Three different sensitization patterns were found: 2 patients had positive STs with BP-OL, 2 patients had a positive STs with both amoxicillin (AX) and PPZ-TZB, and 7 patients had positive STs or DPT exclusively with PPZ-TZB.

TABLE I. Concentrations employed for skin testing with beta-lactams and drug provocation test (DPT) with piperacillin-tazobactam

Reagent	Concentration
Benzylpenicilloyl-octa-L-lysine (BP-OL); DAP-Diater Madrid, Spain	0.04 mg/mL
Benzylpenilloate (DM); DAP-Diater Madrid, Spain	0.5 mg/mL
Benzylpenicillin (BP); Penibiot, Laboratorios Normon SA, Madrid, Spain	10,000 UI/mL
Amoxicillin (AX); Clamoxyl, GSK, Madrid, Spain	20 mg/mL
Cefuroxime (CX); Cefuroxima Normon, Laboratorios Normon SA, Madrid, Spain	2 mg/mL
Meropenem (MERP); Meropenem, Laboratorios Ranbaxy, SL, Barcelona, Spain	1 mg/mL
Piperacillin-tazobactam (PPZ-TZB); Piperazilina/Tazobactam, Aurovitas, Madrid, Spain	20/2.5 mg/mL
DPT with piperacillin-tazobactam (2 g/0.25 g)	
Dilute 2 g PPZ/0.25g TZB in 10 mL of saline 0.9%	
Intravenous administration of:	
(1) Placebo (50 mL of saline 0.9%) in 20 min	
(2) 10% of the dilution + 50 mL of saline 0.9% in 20 min	
(3) 20% of the dilution + 50 mL of saline 0.9% in 20 min	
(4) 20% of the dilution + 50 mL of saline 0.9% in 20 min	
(5) 50% of the dilution + 50 mL of saline 0.9% in 20 min	
Doses are administered every 45 min followed by a final observation period of 60 min	

TABLE II. Characteristics of the patients and results of the allergy study

Patient number	Pattern group	Sex	Age	Reactions	Indication	Latency period/reaction duration	Skin tests	Specific IgE	DPT	Alternative tolerance	Previous tolerance
1	(A)	Male	68	Urticaria	Diverticulitis	5 min/30 min	BP-OL(+) ID with systemic reaction PPZ-TZB (ND)	PENG (0.69 kU/L) AX (0.56 kU/L) tIgE (21.7 kU/L)	ND	ND	UNK
2	(A)	Female	77	Anaphylaxis (eye and palm pruritus, generalized erythema, nasal congestion)	Diverticulitis	5 min/1 h	BP-OL, BP, AX, PPZ-TZB(+) ID 1/10	PENG(–) AX (1.89 kU/L) tIgE (105 kU/L)	ND	ND	AX-CLV, CX
3	(B)	Male	40	Anaphylaxis (nausea, vomiting, hypotension, eyelid edema)	Infectious colitis	10 min/1 h	PPZ-TZB(+) ID 1/10	AX (0.73 kU/L) tIgE (ND)	ND	ND	AX, CLV
4	(B)	Male	67	Anaphylaxis (itching, rash, dyspnea, dizziness, hypotension)	Fournier gangrene	10 min/2 h	PPZ-TZB, AX (+) ID	ND	ND	CX, MERP	UNK
5	(C)	Male	64	Anaphylaxis (Itchy throat, aphonia, dyspnea, stridor, hypotension, wheezing, hives)	Urinary sepsis	5 min/1.5 h	PPZ-TZB (prick 1/100)	ND	ND	CX, MERP	UNK
6	(C)	Female	50	Urticaria	Septic shock	10 min/2 h	PPZ-TZB(+) ID	ND	ND	MERP, AX-CLV	UNK
7	(C)	Female	66	Urticaria	Febrile neutropenia	15 min/45 min	PPZ-TZB(+) ID	ND	ND	CX, MERP, AX-CLV	UNK
8	(C)	Female	52	Urticaria	Pancreatitis	10 min/2 h	PPZ-TZB(+) ID	AX(–) tIgE (ND)	ND	CX, MERP, AX-CLV	AX
9	(C)	Male	49	Anaphylaxis (dyspnea, hypotension, wheezing, exanthema)	Acute myeloblastic leukemia	10 min/2 h	PPZ-TZB(+) ID 1/10	ND	ND	CX, MERP, AX-CLV	AX, AX-CLV
10	(C)	Male	77	Urticaria	Cholangitis, cholecystitis	15 min/30 min	NEGATIVE(–)	PENG(–), AX(–) tIgE (ND)	Urticaria, 800 mg	CX, MERP	AX, CX
11	(C)	Female	71	Urticaria	Respiratory infection	20 min/4 h	NEGATIVE(–)	ND	Urticaria, 1000 mg	CX, MERP	UNK

AX, Amoxicillin; AX-CLV, amoxicillin-clavulanic acid; BP-OL, benzylpenicilloyl-octa-L-lysine; CX, cefuroxime; DPT, drug provocation test; ID, intradermal reaction; MERP, meropenem; ND, not done; PENG, penicillin G; PPZ-TZB, piperacillin-tazobactam; tIgE, total IgE; UNK, unknown.

In those patients with positive STs with BP-OL, DPTs were not performed. Of the 2 patients that had positive STs with AX and PPZ-TZB, in one of them, no further DPTs were performed; the other patient tolerated cefuroxime (CX) and meropenem (MERP).

Finally, all 7 patients who showed a selective pattern to PPZ-TZB underwent a DPT with MERP. All tolerated a therapeutic dose. In 6 of these 7 patients, a DPT was performed with CX, and in 4 of 7, with AX-clavulanic acid. All patients tolerated these drugs.

To our knowledge, this is the largest series of immediate hypersensitivity reactions to PPZ-TZB. Most patients were diagnosed by STs, although 2 patients were diagnosed by DPTs. This suggests the usefulness of STs in the diagnosis of immediate hypersensitivity to PPZ-TZB.

Three patients (27.3%) had positive specific IgE to penicillin G and/or AX. In addition, we were able to identify 3 response phenotypes: group A, which included patients who recognized the BL ring (18.2%); group B, which included patients sensitized to both AX and PPZ-TZB (18.2%) who tolerated CX and MERP; and group C, which included patients with selective hypersensitivity to PPZ-TZB (63.6%).

Group A patients seem to be sensitized to the BL ring. The recommendation so far would be to avoid BLs, although they could probably tolerate MERP, provided they had negative STs.^{6,9} Group B patients are purportedly sensitized to the lateral chain of aminopenicillins, so the possibility of cross-reactivity to aminocephalosporins exists. They tolerated notwithstanding MERP and CX. Group C patients seem to be selective to PPZ-TZB, because they had negative STs to all tested BLs and tolerated several different BLs. Nevertheless, not all BLs were tested.

There are very few reports of immediate hypersensitivity reactions to PPZ-TZB. Gaspar-Marques et al¹ described 1 case of PPZ-TZB anaphylaxis in work environment that had positive STs with BP-OL, CX, and PPZ-TZB; this patient would belong to group A. Rank and Park² reported an anaphylactic reaction with PPZ-TZB during DPT despite the fact that STs with PPZ-TZB had been negative. This also happened to 2 of our patients. Finally, Romano et al³ described a selective hypersensitivity reaction to PPZ in a patient with positive STs with PPZ who tolerated other BLs. This patient would belong to group C.

The main limitations of our study are its retrospective nature, which can be partially circumvented because all patients underwent the same protocol, and the small number of patients. The few existing publications notwithstanding describe 1 or 2 patients at most. Another limitation is the fact that PPZ is formulated with TZB and it was not possible to test them separately, so it cannot be discarded that some patients could be sensitized to TZB or to both PPZ and TZB. Finally, the described sensitization phenotypes are based on a small number of patients, so further confirmatory studies are needed.

In conclusion, STs were useful in the diagnosis of immediate reactions to PPZ-TZB. Furthermore, we found 3 phenotypes of sensitization to PPZ-TZB: (1) BL ring sensitization,

(2) aminopenicillin side chain sensitization, and (3) selective sensitization to PPZ-TZB.

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